

# Oral Allergy Syndrome

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## ABSTRACT

Oral allergy syndrome (OAS) is defined as the symptoms of IgE-mediated immediate allergy localized in the oral mucosa, and the characteristics depend on the lability of the antigen. Another term used for this syndrome is pollen-food allergy (PFS); the patient is sensitized with pollen via the airways and exhibits an allergic reaction to food antigen with a structural similarity to the pollen (class 2 food allergy). In addition to PFS, latex-fruit syndrome is also well-known as the disease exhibiting OAS. In treating the condition, it must be noted that most but not all symptoms of PFS are those of OAS. In many cases, antigens become edible by heating, but some are resistant to heating. Also, since the exacerbation of atopic dermatitis is occasionally observed after the intake of cooked antigens in asymptomatic individuals, careful inquiry of the history is important in designing the treatment. Immunotherapy against the cross-reacting pollen has also been attempted in PFS.

## KEY WORDS

allergen, allergic rhinitis, food allergy, latex allergy, pollen

## DEFINITION

Oral allergy syndrome (OAS) is a condition characterized by IgE-mediated immediate allergic symptoms restricted to the oral mucosa, which may involve itching, stinging pain, and vascular edema of the lips, tongue, palate, and pharynx with a sudden onset, occasionally accompanied by itching of the ear and feeling of tightness of the throat. Usually, these symptoms gradually resolve. A typical example of OAS is oral mucosal symptoms that appear when a patient with birch pollen allergy has eaten a food of the family Rosaceae (apple, cherry, peach, etc.).

## HISTORICAL CONFUSION

There used to be controversy over the definition of OAS. In 1987, Almot *et al.*<sup>1</sup> first reported allergic symptoms induced by eating a food yielding a positive skin test that are primarily oral mucosal symptoms which occasionally spread to the entire body as OAS. They did not mention whether the patients had pollinosis, and the causative foods included shellfish, fish, and eggs. At that time, the term OAS did not attract much attention, but a report by Ortolani *et al.*<sup>2</sup> in 1988 directed attention toward it. Since the symptoms observed after patients with birch pollinosis ate fruits and vegetables were in agreement with those of OAS

reported by Amlot, they reported 262 pollinosis patients who developed symptoms localized to the oral mucosa caused by the ingestion of fruits and vegetables as cases of "OAS", making the term OAS international.

OAS has become widely known with a new definition, i.e., localized oral symptoms due to a labile allergen observed after patients with pollinosis have eaten a fruit or vegetable. This historical background led to confusion among researchers concerning the definition. In 1994, Liccardi *et al.*<sup>3</sup> reported oral symptoms without generalized symptoms caused by the ingestion of eggs or egg-containing foods in a patient with no pollinosis as OAS. In response to this, Kelso<sup>4</sup> stated that the condition might have been usual egg allergy rather than OAS, because the patient had a history of egg-induced hypotension. Liccardi *et al.* responded that the hypotension record was inappropriate as it was based on the self-judgment of the patient, and argued that no generalized symptom was observed on any of the confirmation challenge test using egg.

To avoid such confusion related to the term OAS, food allergy due to a cross-reaction between pollen antigen and fruit or vegetable antigen has been called the more specific term "pollen-food allergy syndrome (PFS)"<sup>5,6</sup>.

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**Table 1** Characteristics of class 1 and 2 food allergy

	Class 1	Class 2
Sensitization to allergens	Gastrointestinal tract	Respiratory exposure
Age of peak prevalence	Early childhood	After school age
Symptoms	Rapid onset of gastrointestinal responses (nausea, abdominal pain, cramp, vomiting, diarrhea); other target organ responses (e.g., skin, respiratory tract) often involved	Mild pruritus, tingling, and/or angioedema of the lips, palate, tongue or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms
Typical foods	Egg, milk, wheat, peanut, fish	Fruit, vegetable
Stable or labile in presence of heat, acid, and proteases	Stable	Labile
Diagnosis	Clinical history and positive SPT responses or CAP-RAST results Oral challenge-positive on double-blinded food-challenge test	Clinical history and positive SPT responses (prick-plus-prick method) Oral challenge-positive with fresh food, negative with cooked food
Treatment	Elimination diet	Elimination diet Foods may become edible by heating Immunotherapy to treat the pollen-induced rhinitis may improve PFS

**Table 2** Major fruits and vegetables reported to show cross-reactivity with pollen

Pollen	Food
Birch	Rosaceae (apple, pear, sweet cherry, peach, plum, apricot, almond), Apiaceae (celery, carrot), Solanaceae (potato), Actinidiaceae (kiwifruit), Betulaceae (hazelnut), Anacardiaceae (mango), Chili pepper, etc.
Japanese cedar	Solanaceae (tomato)
Mugwort	Apiaceae (celery, carrot), Anacardiaceae (mango), spice, etc.
Grass	Cucurbitaceae (melon, watermelon), Solanaceae (tomato, potato), Actinidiaceae (kiwifruit), Rutaceae (orange), Fabaceae (peanut), etc.
Ragweed	Cucurbitaceae (melon, watermelon, cantaloupe, zucchini, cucumber), Musaceae (banana), etc.
Plane	Betulaceae (hazelnut), Rosaceae (apple), lettuce, corn, Fabaceae (peanut, chickpea)

## CHARACTERISTICS OF OAS: CLASS 1 AND CLASS 2 ALLERGY

Food allergens that induce OAS rapidly dissolve in the oral cavity and are readily broken down by digestive enzymes such as those in gastric juice. Since these food allergens differed in properties from known food allergens that are resistant to digestive enzymes and induce sensitization via the intestine, allergy to proteins in fruits and vegetables cross-reactive with pollen antigen in individuals sensitized by the antigen via the airway began to termed class 2 food allergy<sup>7</sup> to distinguish it from food allergy caused by conventional intestinal sensitization (class 1 food allergy) (Table 1, 2).

## DISEASES EXHIBITING OAS

PFS mentioned above is a typical disease that exhibits OAS. In addition to PFS, latex-fruit syndrome (LFS; allergy to fresh fruits or vegetables after sensitization with latex-inhalation antigen in latex powder) has been reported as disease exhibiting OAS. Clinically, also, some patients yielding a positive skin test complain of oral discomfort immediately after the ingestion of egg on the oral challenge test but show no

spread of allergic symptoms to the entire body if they continue eating it.

## PFS IS NOT EQUAL TO OAS

While the majority of symptoms of PFS are indeed mild, such as the OAS, caution is necessary, because systemic and severe reactions may be observed by some pollen-related food allergens (Api g 1, Gly m 4). The antigens that cause PFS have been extensively studied, particularly in Western countries, and they will be discussed in the next section.

## ANTIGENS CAUSING OAS

In Europe, more than 70% of patients with birch pollinosis are allergic to pollen-related food allergens such as the apple, cherry, and hazelnut. Major allergens responsible for these symptoms belong to a group exhibiting high-level homology with Bet v 1, a major antigen of birch pollen (Table 3). The next most frequent is the food allergen showing a high-level homology with Bet v 2 (profilin), another birch pollen antigen. Bet v 5 and 6 are also reportedly involved in cross-reactivity, but most cross-reactivity is related to Bet v 1, and the involvement of other antigens is negligible.<sup>8</sup>

**Table 3** Major pollen/latex and class 2 food allergens

Pollen/latex allergens		Class 2 food allergens			
Bet v 1 homolog's (Group belonging PR-10)					
Aln g 1 (alder)	Bet v 1 (birch)	Api g 1 (celery)	Ara h 8 (peanut)	Cor a 1 (hazel)	Dau c 1 (carrot)
Car b 1 (hornbeam)	Cas s 1 (chestnut)	Fra a 1 (strawberry)	Gly m 4 (soybean)	Mal d 1 (apple)	Pru ar 1 (apricot)
Cor a 1 (hazelnut)	Que a 1 (white oak)	Pru av 1 (sweet cherry)	Pyr c 1 (pear)	Sol t 1 (potato)	Vig r 1 (mung bean)
Profilin					
Art v 4 (mugwort)	Bet v 2 (birch)	Ana c 1 (pineapple)	Ara h 5 (peanut)	Api g 4 (celery)	Cap a 2 (bell pepper)
Cyn d 12 (Bermuda grass)	Hel a 2 (sunflower)	Cit s 2 (sweet orange)	Cor a 2 (hazel)	Cuc m 2 (muskmelon)	Dau c 4 (carrot)
Ole e 2 (olive)	Phl p 12 (timothy)	Gly m 3 (soybean)	Lit c 1 (lychee)	Lyc e 1 (tomato)	Mal d 4 (apple)
Hev b 8 (latex)		Mus xp 1 (banana)	Pru av 4 (sweet cherry)	Pru p 4 (peach)	Pyr c 4 (pear)

Data from <http://fermi.utmb.edu/SDAP/>.

### Bet v 1 GROUP

Bet v 1 (PR-10) is one of the pathogenesis-related (PR) proteins, which increase in plants when they are exposed to stress. Many foods have been reported to contain this protein, and the cross-reactivity is considered to be derived from the high-level homology of amino acid sequences in this group. The IgE-binding activities of these allergens are readily lost through heat or enzyme treatment. Also, the p-loop (AA41-52) region has been reported to be particularly important in the IgE epitope of Bet v 1.<sup>9</sup>

While many of the symptoms caused by antigens of PR proteins are those of OAS, antigens of celery (Api g 1) and soybean (Gly m 4), which belong to the same group as Bet v 1, have been reported to induce marked systemic symptoms.

### Api g 1

Celery allergy is common in Europe (Primarily Switzerland, France, and Germany). In Switzerland, it is reported to be a major cause of food-induced anaphylaxis,<sup>10</sup> and about half of the patients have been reported to show systemic allergic reaction.<sup>11,12</sup> Its allergenicity is not changed markedly by heating. Pollen of birch and mugwort is known to be cross-reactive to celery, and is considered to be a sensitizing antigen.<sup>13</sup> While celery allergens include Api g 4 and Api g 5, the major allergen is Api g 1, which belongs to the above-mentioned PR-10. However, the reason why Api g 1 is stable against heating unlike other allergens belong to the same group as Bet v 1 has not been sufficiently clarified. Wangorsch *et al.*<sup>14</sup> reported that Api g 1 has 2 isoforms, that Api g 1.01 shows a stronger IgE-binding capacity than Api g 1.02, and that this difference is derived from the fact that the binding site of Api g 1.01 in the above p-loop

region is Lys44 while that of Api g 1.02 or Bet v 1 is Glu45, and suggested the importance of this region.

### Gly m 4

In 2002, Kleine-Tabbe *et al.*<sup>15</sup> reported that 20 patients with birch pollinosis developed allergic symptoms including serious ones after the initial ingestion of soybean protein food. Notable symptoms included swelling of the face (17 patients), OAS (14), dyspnea (6), urticaria (6), and drowsiness (5). They also reported that soybean starvation-associated message 22 (SAM22: Gly m 4), which belongs to PR-10, showed an IgE-binding capacity in 85% (17/20) of the patients. A follow-up study by Mittag *et al.*<sup>16</sup> confirmed that Gly m 4-specific IgE was positive in 21 of 22 birch pollinosis patients who developed soybean allergy, and that it inhibited the binding of IgE to soybean protein by 60% or more in 9 of 11 patients, indicating that Gly m 4 was the major allergen. Moreover, as the binding of IgE to soybean protein was inhibited by 80% or more by the addition of birch pollen protein in 9 of the 11 patients, they suggested that birch pollen is primarily responsible for the common antigenicity of the two. According to their report, Gly m 4 was not detected in fermentation products such as miso and soy sauce or roasted soybean, but its content was 9 ppm in tofu, 11 ppm in soy flakes, 70 ppm in a dietary powder among soybean-containing food despite its variation with the total soybean content. They also reported that Gly m 4 concentration was markedly affected by the cooking method and that it was reduced by 30-minutes and not detected after 4-hour heating. Three patients with alder/birch pollinosis who developed OAS (1 case) or anaphylaxis (2 cases) after the intake of soymilk have been reported, and an involvement of Gly m 4 is suspected<sup>17</sup> in Japan, too.

**Table 4** Lipid transfer protein (LTP); major allergens belonging to PR-14

Inhaled allergens		Food allergens		
Tree	Weed	Fruits/vegetables	Beans/nuts/seeds	
Cas s 8 (chestnut)	Art v 3 (mugwort)	Aspa o 1 (asparagus)	Bra o 3 (cabbage)	Cor a 8 (hazelnut)
Pla a 3 (plane tree)	Par j 1 (pellitory)	Cit l 3 (lemon)	Cit s 3 (sweet orange)	Jug r 3 (English walnut)
	Par j 2 (pellitory)	Fra a 3 (strawberry)	Lac s 1 (lettuce)	
	Par o 1 (pellitory)	Lyc e 3 (tomato)	Mal d 3 (apple)	
		Pru ar 3 (apricot)	Pru av 3 (sweet cherry)	
Heb b 12 (latex)		Pru d 3 (European plum)	Pru p 3 (peach)	
		Vit v 1 (grape)	Zea m 14 (maize, corn)	

Data from <http://fermi.utmb.edu/SDAP/>.

### PROFILIN GROUP

Profilin is considered to be an allergen involved in a wide range of cross-reactivities among plants, and patients sensitized with it react with a variety of plants and foods. For example, it is considered responsible for the cross-reactions between birch/mugwort pollen-celery-spices, grass pollen-celery-carrots, and tree pollen-hazelnut. The cross-reactivity of IgE is considered to be due to a structural similarity rather than similarity at the amino acid sequence level.<sup>18</sup> There major IgE epitope have been identified in birch profilin.<sup>19</sup>

Asero *et al.* performed skin tests in 200 pollinosis patients using purified palm profilin (Pho d 2) and observed positive reaction in one-third of the patients. They were also positive for pollen from a wide range of plants, more than half of them exhibited OAS with symptoms of fruit allergy, and no symptom was induced by cooked or processed foods.<sup>20</sup>

### CROSS-REACTIVE CARBOHYDRATE DETERMINANTS (CCD)

Carbohydrates that act as cross-reacting antigens among various plants or invertebrates are collectively called cross-reactive carbohydrate determinants (CCD).

Carbohydrates with an IgE-binding capacity have also been reported in plant proteins with no allergenicity. They are, for example, bromelain of pineapple, horseradish peroxidase (HRP), polyamine oxidase of corn, ascorbic acid oxidase of *Cucurbita pepo*, and phytohemagglutinin of haricot bean. Many CCDs are monovalent and do not form bridges of IgEs on the mast cells, and so they are generally considered not to induce histamine release. However, it has been revealed that about half of individuals positive for Ole e 1, a major antigen of Olive pollen, show IgE antibodies to this carbohydrate, and that this carbohy-

drate induces histamine release in them.<sup>21</sup>

Recently, van Ree *et al.*<sup>22</sup> reported that  $\alpha$ 1,3-fucose and  $\beta$ 1,2-xylose, which are N-linked glycans, have IgE-binding capacities. Individuals are considered to be sensitized when exposed to pollen and thereafter develop cross-reaction to foods. However, only limited individuals with IgE antibodies to CCDs actually develop clinical symptoms, and whether they develop symptoms is speculated to depend on the difference in the glycan number or affinity of IgE antibodies.<sup>23</sup>

### LIPID-TRANSFER PROTEINS (LTP) GROUP

Antigens belonging to the LTP family have been reported to exist in a wide variety of fruits, vegetables, and pollen (Table 4).

LTP, belonging to PR-14, exhibit an antigenicity resistant to heating or digestive enzymes and cause fruit allergy even without pollinosis, and the symptoms are not only OAS but also involve severe systemic symptoms at a relatively frequent rate. Therefore, they are presently considered to be non-pollen-related allergens (class 1 food allergens) that act by intestinal sensitization.<sup>24</sup> However, there are data that suggest that LTP is responsible for food allergy associated with pollinosis (class 2 food allergy) in some patients.

Mugwort is known to be a major cause of pollinosis in Mediterranean coastal areas, and Art v 3 is a mugwort pollen antigen belonging to the LTP group. According to a report on cross-reaction between Art v 3 and LTP from peach or apple,<sup>25</sup> whether the cross-reaction was due to sensitization primarily by pollen or peach was unclear. To study this relationship, Pastorello *et al.*<sup>26</sup> collected 17 patients with peach allergy and compared 10 who had not developed pollinosis and 7 with pollinosis. The 10 patients with no pollinosis reacted with mugwort pollen LTP and peach LTP, but the 7 pollinosis reacted with proteins other than

LTP. Next, the reactions of IgE with mugwort pollen LTP and peach LTP were examined using pooled serum from 10 patients by immunoblot inhibition. IgE binding to the peach 9-kDa band (LTP) was totally inhibited by a small amount of peach LTP but only by 100 times amount of mugwort LTP, whereas a small amount of both mugwort and peach LTP totally inhibited the IgE-binding to mugwort LTP. Therefore, they concluded that this cross-reactivity was primarily due to sensitization by peach LTP (peach class 1 allergy). In contrast, Lombardero *et al.*<sup>27</sup> considered that the report by Pastorello *et al.* was biased based on the fact that the patients were mostly those with peach allergy, and performed reevaluation by collecting 24 patients with mugwort pollinosis. They reported that more than 70% of the patients were positive on the skin test to mugwort LTP. They subsequently evaluated the cross-reactivity of mugwort LTP with peach LTP by ELISA inhibition, and reported that IgE binding with peach LTP was inhibited by the addition of mugwort LTP in 3 of 6 studied patients but that IgE binding with mugwort LTP was not inhibited by the addition of peach LTP, suggesting that the common antigenicity of mugwort and peach LTP was primarily due to mugwort pollen in some patients (class 2 food allergy).

## OAS IN JAPAN

In Japan, also, there have been reports of OAS due to foods of the family Rosaceae in patients hypersensitive to birch pollen in Hokkaido and *Alnus sieboldiana* (family Betulaceae, genus *Alnus*) pollen in Hyogo Prefecture.<sup>28,29</sup>

The frequency of OAS in patients with Japanese cedar pollinosis is lower than that in those with birch pollinosis (75%), being reported to be 7-17%.<sup>30,31</sup> According to questionnaire surveys performed in Japanese cedar pollinosis patients, melon and kiwifruit induced allergy in many of them.

According to our oral questionnaire survey concerning foods causing fruit and vegetable hypersensitivity in patients with Japanese cedar pollinosis (17 respondents with pollinosis and fruit allergy), melon (12/17), kiwi (9/17), tomato (9/17), watermelon (7/17), and pineapple (6/17) were frequently ingested. However, in such a questionnaire survey, reactions to materials with pharmacological actions contained in foods may be misinterpreted by the respondents as allergic symptoms, and food allergy unrelated to Japanese cedar pollinosis may be reported; therefore, the competitiveness for IgE antibody between cedar pollen and fruit or vegetable antigen must be demonstrated.

At first, we identified the main allergens of tomato fruit,<sup>32</sup> then demonstrated the cross-reactivity between tomato fruit and Japanese cedar pollen by RAST inhibition, and further identified the protein responsible for the cross-reactivity by immunoblot inhibition.<sup>33</sup>

As a result of comparing the amino acid sequences of these proteins, we clarified the presence of regions showing close agreement, i.e., Cry j 2 of Japanese cedar pollen and PG2A of tomato fruit, and reported the possible involvement of these regions in the competitiveness for IgE. Concerning the common antigenicity of tomato and Japanese cedar pollen, there is a report that symptoms considered to be OAS appeared after the oral ingestion of tomato in a dog model of Japanese cedar pollinosis, establishing the cross-reactivity between Japanese cedar pollen and tomato fruit antigens.<sup>34</sup>

## TREATMENT FOR OAS

In PFS due to birch pollinosis, birch pollen-specific immunotherapy has been reported to be effective for the treatment of OAS to related foods.<sup>35,36</sup> Food tolerance and negative skin tests have also been reported to persist for 30 months,<sup>37</sup> and food skin tests converted to positive with the reactivation of OAS symptoms in all patients.

Foods that cause OAS should be avoided, in principle, but pollen-associated foods are often edible when heated. Therefore, the unnecessary elimination of foods should be avoided through close evaluation of the history of allergy due to cooked foods and oral challenge test. There is also a report that symptoms of OAS were significantly alleviated using antihistamines compared with a placebo.<sup>38</sup> Antihistamines might partially relieve symptoms of oral allergy syndrome.

However, some pollen-related foods such as celery and soybean may lead to severe symptoms although they belong to the Bet v 1 group. In LFS, the antigenicity of some foods is not lost by heating, and they tend to cause severe symptoms.

Naturally, PFS may also cause generalized symptoms and even anaphylaxis if a large amount of antigen has been ingested. Therefore, in case of emergency, patients with a history of anaphylaxis should carry a portable epinephrine injection kit, antihistamines, and oral steroids with a medical certificate.

Even if cooked food allergens did not elicit oral allergy syndromes, they may cause T-cell-mediated late-phase reactions (deterioration of atopic eczema) in some birch pollen-allergic patients with atopic dermatitis. Because thermal processing affected their conformational structure and not the primary amino acid sequence. Therefore, the judgment of whether the intake of cooked foods may be permitted should not be made on the basis of the presence or absence of immediate hypersensitivity alone.<sup>39</sup>

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